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The β-adrenergic antagonist propranolol partly abolishes thermogenic response to bioactive food ingredients

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Abstract

A combination of tyrosine, capsaicin, catechins, and caffeine has been shown to possess a thermogenic effect in humans. The present objective was to investigate whether the thermogenic response to the bioactive combination (BC) could be diminished or abolished by propranolol. Twenty-two men (age, 29.0 ± 7.1 years; body mass index, 26.0 ± 3.6 kg/m^2; mean ± SD) participated in a 4-way, randomized, double-blind, placebo-controlled crossover study. The effect of the following was tested: (1) placebo, (2) BC, (3) BC + 5 mg propranolol, and (4) BC + 10 mg propranolol. Resting metabolic rate, respiratory quotient, and the thermogenic response were measured for 5 hours postintake. Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and appetite ratings were assessed every half hour. The BC increased resting metabolic rate by 5% (73 [36; 110] kJ/5 h, mean [95% confidence interval], $P < .0001$) compared with placebo. Both propranolol doses blunted the thermogenic response by 50% compared with placebo ($P < .01$). The BC increased SBP by 3% (4 ± 1 mm Hg, $P = .003$) compared with placebo. The effect of BC on SBP was reduced by 25% by propranolol ($P = .07$). The BC (with or without propranolol) increased DBP by 6% (4 ± 1 mm Hg, $P \leq .0002$). Propranolol decreased heart rate by 5% (3 ± 1 beats per minute, $P < .0001$) compared with placebo and BC. No effects were observed on appetite ratings. In conclusion, the study confirms the thermogenic properties of BC. The 50% reduction of the thermogenic response by propranolol indicates that β-adrenergic pathways are partly responsible for the thermogenic response.

1. Introduction

In an attempt to understand the development of the current obesity epidemic, studies have estimated the magnitude of surplus in daily energy balance required for the apparent chronic weight gain at population level. Hill et al found that 90% of the population consumes an excess of 209 kJ/d or less [1]. This implies that an intervention that reduces the positive energy balance by 209 kJ/d could offset weight gain in about 90% of the population. Some food ingredients may have a stimulatory effect on energy expenditure (EE) and enhance satiety.

The sympathetic nervous system (SNS) plays an important role in the regulation of EE. Infusions with catecholamines have induced a thermogenic response in humans [2,3]. There are suggestions that obese subjects have an impaired thermogenic response to foods and that an impaired SNS responsiveness might be involved [4]. The effect of catecholamines is modulated through 4 adrenoreceptors, that is, by stimuli of β_1-, β_2-, and β_3-adrenoreceptors, and inhibition of α_2-adrenoreceptors. Especially β_1- and β_2-adrenoreceptors are thought to mediate the thermogenesis in humans [5], whereas β_3-agonists and -antagonists only have a rather weak effect [6,7]. Noradrenaline (NA) stimulates and increases sympathetic activity, which causes suppression of hunger and enhances satiety and EE, which is covered in part by increased fat oxidation [7-9].

We have previously tested the thermogenic effect of a combination of capsaicin, green tea extract (GTE), caffeine, tyrosine, and calcium and showed that the supplement induced a 2% to 3% thermogenic response in humans and that the effect was maintained after an 8-week supplementation [10,11]. Capsaicin added to meals have been observed to increase EE and fat oxidation [12,13] and decrease appetite,

The dietary supplements containing the ingredients examined in the present paper are not commercially available. No authors have any financial or personal interest in the dietary supplements.

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probably by stimulating sensory pathways in the mouth and in the gastrointestinal regions, leading to sympathetic stimulation [14,15]. Catechins from GTE, especially polyphenol catechin epigallocatechin gallate, have been associated with an increase in sympathetic stimulation, thermogenesis, and fat oxidation in humans [16-18], though with some inconsistencies [16,19]. The effect of caffeine on appetite and thermogenesis is measurable but rather weak [20-24]. Caffeine seems to be a potent thermogenic amplifier when given in conjunction with other SNS agonists such as ephedrine, catechins, or capsaicin [17,22,25-27]. In addition, tyrosine supplementation together with other sympathomimetics increased temperature in the brown adipose tissue in rodents and decreased food intake in a synergistic fashion [28-30]. The rationale for combining the above ingredients is that the effects of the compounds may be potentiated in a synergistic fashion. Capsaicin has been found to activate the sympathetic nerves by stimulating NA release into the synaptic cleft where NA interacts with the adrenergic receptors [31]. However, the adrenergic receptor stimulation of NA is short-lived because NA is rapidly removed by catechol *O*-methyltransferase. Catechins inhibit the enzyme [25,32] and may prolong the effect of capsaicin. Sympathetic nervous system activity is dependent on the production of cyclic adenosine monophosphate (cAMP). The cAMP response is short-lived, but can be prolonged by an intake of caffeine. Caffeine may also, as an adenosine antagonist, block the inhibitory effect of adenosine on further NA release [33]. Such compounds may be of value in the prevention of weight gain and regain. We have previously found that 8 weeks of chronic treatment produced 1 kg less body fat regain than placebo [11].

The present objective was to investigate whether the sympathetic stimulation of EE after the intake of a combination of capsaicin, GTE, caffeine, and tyrosine could be blunted when combined with the β-adrenergic receptor blocker propranolol. This was investigated by measuring the acute effect on EE, substrate oxidation, and ad libitum energy intake (EI) after intake of the supplement given alone or in combination with 5 or 10 mg of propranolol.

2. Methods and materials

2.1. Subjects

Twenty-three healthy, normal-weight to obese men (age, 29.0 ± 7.1 years; body mass index [BMI], 26.0 ± 3.6 kg/m^2) were recruited in the study. Only 22 subjects completed the study, as 1 participant dropped out because of failure to follow the protocol (age, 22 years; BMI, 25.3 kg/m^2). The 22 subjects were divided into 2 groups: normal weight (BMI, 18.5-25 kg/m^2) and overweight/obese (BMI, 25-35 kg/m^2) (Table 1). They were weight stable (±3 kg in the last 3 months), nonsmoking, and nonathletic; had no use of dietary supplements or frequent use of medication; were not asthmatics; and had no history of heart disease or abnormal electrocardiogram (ECG) result. All participants had height, body weight, blood pressure, heart rate (HR), and ECG measured before study inclusion. Inclusion criteria included a blood pressure less than 165/95 mm Hg and a clinically normal ECG result. The subjects followed a normal Danish habitual diet, with rare use of hot spices, and avoided extreme intakes of coffee/tea. Frequency of caffeine intake was not an exclusion or inclusion criterion. The subjects were recruited by an advertisement on a recruitment Web page and student Web pages. All subjects gave their written consent after having received verbal and written information about the study. The study was in accordance with the Helsinki II Declaration and was approved by The Municipal Ethical Committee of Copenhagen and Frederiksberg.

Table 1
Physical characteristics (mean ± SD) for the normal-weight subgroup, overweight subgroup, and the pooled total group

	Normal-weight subgroup (n = 11)	Overweight subgroup (n = 11)	Pooled group (n = 22)
Age (y)	26.8 ± 4.4	31.7 ± 8.6	29.3 ± 7.1
Body weight (kg)	77.0 ± 6.5	95.9 ± 11.7	86.5 ± 13.3
BMI (kg/m^2)	23.3 ± 1.6	28.9 ± 2.9	26.1 ± 3.6
FM (kg)	10.0 ± 2.5	21.9 ± 7.8	15.9 ± 8.3
FM (%)	12.9 ± 2.7	22.3 ± 5.9	17.6 ± 6.6
FFM (kg)	67.0 ± 5.2	74.1 ± 6.2	70.5 ± 6.6
FFM (%)	87.1 ± 2.7	77.7 ± 5.9	82.4 ± 6.6

Data were analyzed using mixed model analysis of variance. Post hoc comparisons were made between the periods, with Tukey-Kramer adjustment of significance levels for the pairwise comparison. No significant differences between supplements were observed.

2.2. Experimental design

The present study was designed as a 4-way crossover, randomized (by roman square), placebo-controlled, double-blind study. Each treatment day (single test) was separated by more than 7 days of washout period. All treatments were administered as tablets containing 300 mg cayenne (analogous to 0.8 mg capsaicin and 160.000 Scoville heat units), 1000 mg GTE (whereof 250 mg catechins), 813 mg tyrosine, 200 mg caffeine (100 mg from GTE and 101 mg anhydrous caffeine), or placebo (microcrystalline cellulose) combined with either 5 or 10 mg propranolol (Propranolol DAK; Nycomed, Roskilde, Denmark) or placebo (inert vehicle consisting of lactose monohydrate and talcum powder). Combinations of treatments are as follows:

PL: placebo for BC + placebo for propranolol
BC: bioactive compound + placebo for propranolol
BC + 5 mg: bioactive compound + 5 mg propranolol
BC + 10 mg: bioactive compound + 10 mg propranolol

Propranolol is a nonselective adrenergic β-receptor antagonist without intrinsic sympathomimetic effect and with some membrane-stabilizing effect. The placebo tablets could not be distinguished from the bioactive compound or propranolol, respectively, with regard to color, taste, smell,

or appearance. The subjects were instructed not to change their dietary and beverage habits (including intake of coffee and tea), use of spices, level of physical activity, smoking habits, and use of medication throughout the study period.

2.3. Respiratory measurements

On each test day, the subjects arrived at the department at 7:00 AM. After voiding (emptying bladder), body weight was measured to the nearest 0.05 kg on a decimal scale (Lindeltronic 8000, Copenhagen, Denmark); and height, to the nearest 0.5 cm. Body composition, fat-free mass (FFM), and fat mass (FM) were estimated by bioelectrical impedance analysis using an Animeter (hydration/body composition monitoring unit, Quadscan 4000; Bodystat, Douglas, United Kingdom). Heart rate and blood pressure were measured using an automatically inflating cuff (digital blood pressure meter model UA-743; A and D, Tokyo, Japan). All participants were asked on each test day about their general well-being and if they had any illness or adverse effects of the treatment since their last visit. After anthropometric assessment, the subjects rested for at least 1/2 hour in a supine position before they underwent assessments of resting metabolic rate (RMR) and respiratory quotient (RQ) by indirect calorimetry using a ventilated hood system (Oxycon Champion; Mijnhardt, Bunnick, the Netherlands) as described in detail elsewhere [22]. Resting metabolic rate was calculated using a formula assuming a fixed protein catabolism [34], as the error of calculating RMR by omitting the exact correction from urinary nitrogen is negligible and too uncertain to estimate for a short period. The precision of the ventilated hood system was validated by an alcohol burning test on a weekly basis; the coefficient of variation was 1.5%.

The respiratory measurements were of 6-hour duration, from 8:00 AM to 2:00 PM. To secure to some extent adrenergic β-receptor blocking before ingestion of the bioactive test compound, the subjects ingested the propranolol tablets or its placebo at 8:00 AM (1 hour before the test compound) together with 100 mL tap water. Immediately thereafter, 2 baseline measurements (2 × 25 minutes) were performed between 8:00 and 9:00 AM. At 9:00 AM, the participants ingested the bioactive compound or its placebo together with 100 mL tap water; and 25-minute respiratory measurements were repeated 10 times over the next 5 hours (postdose). Blood pressure and HR were assessed every half hour from 8:00 AM to 2:00 PM. The participants had been instructed to fast except for 1/2 L of water from 10:00 PM on the evening before the measurement. They also refrained from drinking water in the last hour before the respiratory measurement to avoid confounding by raising SNS activity, sympathetic vasoconstrictor activity, or/and cardiac vagal tone [35]. The subjects had been instructed to refrain from taking medication, alcohol, caffeinated coffee/tea, and chocolate and from performing energetic physical activity for 24 hours before the respiratory measurements. To limit diurnal variation and inter-/intrasubject variations, all measurements were carried out according to an identical time schedule. The subjects were instructed not to undertake hard physical activity until 6 hours after the end of each test day. This was included in the protocol to prevent the subjects from becoming unwell during physical activity because of the inhibitory effect of propranolol on hemodynamics.

2.4. Subjective appetite sensations

Visual analogue scales (VAS) were used to monitor each subject's appetite sensations before and after intake of the test compound. Composition of VAS was a line (100 mm in length) with words anchored at each end expressing the most positive and the most negative rating of the subjects' sensations of hunger, satiety, prospective consumption, fullness, and desire to eat something sweet, salty, or rich in fat or to eat meat/fish. The subjects were instructed to complete VAS every half hour between 7:30 AM and 2:00 PM.

2.5. Ad libitum EI

The subjects were given an ad libitum brunch, 5 hours postintake of the bioactive treatment or its placebo, at completion of respiratory measurements on each test day. The ad libitum meal was a 1329-g pasta salad lunch (610 kJ/100 g; macronutrient composition: protein, 15.3 E%; carbohydrate, 54.6 E%; and fat, 30.1 E%). The subjects were instructed to eat at a constant pace and to stop eating when they felt satiated. Ad libitum EI was assessed from the amount of the meal consumed. Immediately after completion of the meal, the subjects rated their sensation of hunger, satiety, prospective consumption, fullness, and desire to eat something sweet, salty, or rich in fat or to eat meat/fish by the above-described VAS. Furthermore, the subjects rated their opinion of organoleptic quality of the meal by VAS in regard to appearance, smell, taste, aftertaste, and general palatability of the meal.

2.6. Statistical analysis

All descriptive data are given as mean ± SD. All results are given as mean and SE or 95% confidence interval. The level of significance was set at less than .05. Statistical analyses were performed with SAS 8.2 (SAS Institute, Cary, NC). All data were analyzed based on intention to treat. Before the statistical analysis, all data were tested for normality by Shapiro-Wilk W test and variance homogeneity and were data-transformed if necessary. Differences between treatments were tested by analysis of covariance with weight groups (normal weight vs overweight/obese) as class variable. However, no significant difference was found between the 2 groups with regard to the thermogenic and hemodynamic effect of the bioactive supplement. Thus, the 2 groups were analyzed as 1 group. Differences between treatments were tested with or without adjusting for various confounders such as previous treatment, period, and anthropometric measures. Post hoc comparisons were made, with Tukey-Kramer adjustment of significance levels for the pairwise comparison, using unpaired t test when the analysis indicated significant treatment effect. Respiratory

measurements (5-hour RMR and RQ) were tested by mixed linear models procedure as repeated measurement adjusted for baseline level.

It was not possible to transform data to achieve normal distribution and/or variance homogeneity of VAS ratings of appetite sensations. Data were therefore calculated as an area under the curve (dAUC) after subtraction of the baseline level ratings and tested by analysis of variance (mixed linear models).

The relationship between 5-hour RMR (dAUC) and anthropometric measures was tested in a Pearson correlation test for all subjects (N = 22) and in the 2 subgroups (normal weight and overweight/obese). Spearman correlation test was used if normality could not be reached.

Blood pressure and HR were calculated as mean value of the repeated measurements and tested by analysis of variance (mixed linear models). The relationship between changes in 5-hour mean RMR and 5-hour mean hemodynamic measures during the intervention was tested by Pearson correlation test or by Spearman correlation test if normality could not be reached.

3. Results

3.1. Body weight and composition

There were no significant differences between treatments in body weight, BMI, FM, or FFM.

3.2. EE and RQ

No effect of the propranolol treatment was observed on baseline levels of RMR (placebo, 7515 ± 185 kJ/d; BC, 7453 ± 195 kJ/d; BC + 5 mg, 7410 ± 172 kJ/d; and BC + 10 mg, 7377 ± 145 kJ/d; $P = .4$) and RQ (placebo, 0.83 ± 0.01; BC, 0.82 ± 0.01; BC + 5 mg, 0.82 ± 0.01; and BC + 10 mg, 0.83 ± 0.01; $P = .6$). No effect of period or previous treatment was found on RMR or RQ. The bioactive treatment induced a significantly higher thermogenic response compared with placebo by 73 (36; 110) kJ/5 h (mean [95% confidence interval]) ($P < .0001$) (Fig. 1), which corresponded to a thermogenic response of 5% greater than basal metabolic rate (BMR) baseline value compared with placebo (ie, 24 h/5 h × 73 kJ/5 h / BMR of 7484 ± 188 kJ/24 h [mean ± SE]) (Fig. 1). Intake of 5 and 10 mg propranolol decreased the RMR response of BC by approximately 50% compared with placebo (BC + 5 mg: 39 [12; 66] kJ/5 h, $P = .0002$; BC + 10 mg: 36 [7; 65] kJ/5 h, $P = .002$, respectively). The RMR responses greater than BMR baseline were 2.5% and 2.3% after intake of 5 and 10 mg propranolol, respectively. Both doses of propranolol reduced the thermogenic response significantly compared with the bioactive treatment by 34 (−0.3;69) kJ/5 h ($P < .0001$) and 37 (−0.2; 74) kJ/5 h ($P < .0001$), respectively. No difference in RMR was found between the propranolol treatments ($P = 1.0$).

When testing the linear relationships between 5-hour RMR and anthropometric measures, we found that body weight ($r = −0.46$, $P = .03$) and FM ($r = −0.42$, $P < .05$) correlated to the 5-hour thermogenic response after treatment with the bioactive compound in the total group (n = 22). Otherwise, no relationship was found between 5-hour RMR and anthropometric measures in either the total group or in the 2 subgroups.

No significant difference in RQ (calculated as 5-hour AUC) was observed between treatments (placebo vs BC: 0.03 [−0.03, 0.08], $P = .4$; or placebo vs 5 or 10 mg propranolol: 0.04 [−0.001; 0.08], $P = .4$ and 0.06 [−0.01; 0.12], $P = .1$, respectively).

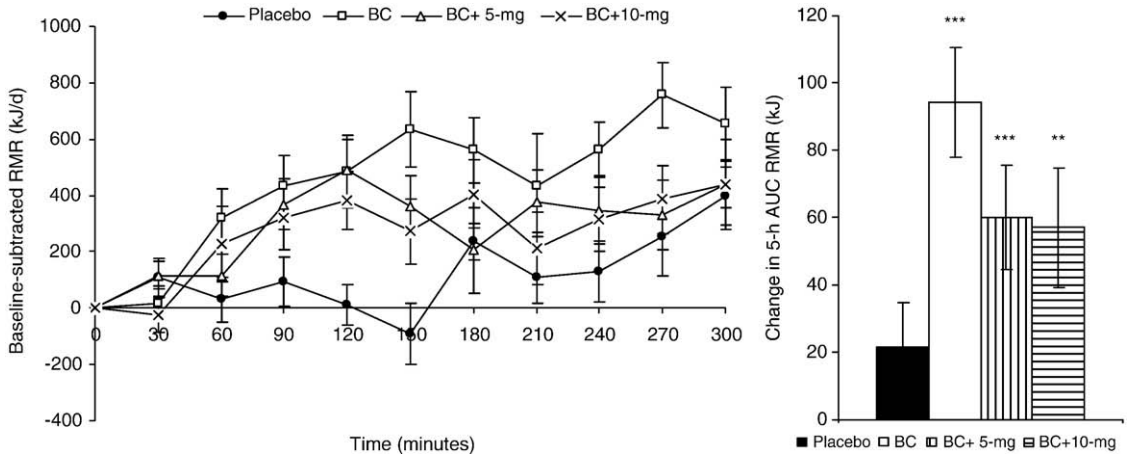

Fig. 1. Baseline-subtracted 5-hour RMR (presented as repeated measurement and AUC) in 22 young normal-weight to overweight men (age, 29.0 ± 7.1 years; BMI, 26.0 ± 3.6 kg/m^2) after treatment with PL, BC, BC + 5 mg, or BC + 10 mg. Data are presented as mean ± SE and were analyzed as repeated measurements and AUC using mixed model analysis of covariance. Post hoc comparisons were made between treatments, with Tukey-Kramer adjustment of significance levels for the pairwise comparison. A significant difference was found between placebo and the bioactive supplement with or without preceding propranolol treatment ($P < .01$).

3.3. Hemodynamic factors

There was no significant difference between treatments in effect on baseline levels of systolic blood pressure (SBP), diastolic blood pressure (DBP), or HR ($P = .7$, $P = .3$, and $P = .5$, respectively). No effect of period or carryover effect was found on SBP, DBP, or HR. The bioactive treatment increased mean SBP by 3% (4 ± 1 mm Hg, $P = .003$) compared with placebo (Table 2). Intake of 5 and 10 mg propranolol decreased the SBP response of the bioactive compound by approximately 25% compared with placebo. However, the propranolol treatments were not significantly different compared with either the bioactive treatment or placebo.

All bioactive treatments, both with and without propranolol, increased mean DBP significantly by 6% (4 ± 1 mm Hg, $P \leq .0002$) compared with placebo (Table 2). No significant difference was found between other treatments.

The propranolol treatments resulted in a 5% decrease in mean HR by 3 ± 1 beats per minute ($P < .0001$) compared with placebo (Table 2). Mean HR response to the bioactive treatment was similar to placebo (0.2 ± 0.6 beats per minute, $P = 1.0$) and was increased compared with the propranolol combined treatments ($P < .001$).

There was a significant linear relationship between the increase in RMR and SBP when the subjects were given the bioactive compound with 10 mg propranolol ($r = 0.6$, $P = .001$). Otherwise, no relationship was found between change in RMR and hemodynamics.

3.4. Subjective appetite sensations

The baseline level of the subjective rating of hunger was significantly decreased when treated with the bioactive compound combined with 5 mg propranolol compared with placebo (47 ± 4 vs 59 ± 4 mm, $P = .01$). No other appetite sensation was significantly affected by treatment at baseline rating. No effect of period or previous treatment was found on any of the subjective ratings of appetite. Sensation of hunger was 60% (dAUC, −46 [9; 83] mm; $P < .05$) lower when the subjects were treated with the bioactive compound combined with 5 mg propranolol compared with placebo. No significant difference in appetite ratings was found between other treatments.

Table 2
The level of baseline-subtracted average change in hemodynamics (between 0 and 5 hours postintake) in 22 young men (mean ± SE)

	PL	BC	BC + 5 mg	BC + 10 mg
SBP, mm Hg	3.1 ± 0.7	7.2 ± 0.9*	5.4 ± 0.9	5.6 ± 0.9
DBP, mm Hg	1.7 ± 0.7	5.6 ± 0.7*	5.9 ± 0.7*	6.0 ± 0.9*
HR, beats/min	0.5 ± 0.7	0.7 ± 0.5	−2.5 ± 0.5*,†	−2.0 ± 0.6*,†

Data were analyzed using mixed model analysis of covariance. Post hoc comparisons were made between the periods, with Tukey-Kramer adjustment of significance levels for the pairwise comparison.

* Significantly different from PL ($P < .05$).

† Significantly different from BC ($P < .05$).

3.5. Ad libitum EI

No effect of period or previous treatment was found on ad libitum EI or subjective ratings of appetite. No significant difference in ad libitum EI was observed between treatments (placebo, 3178 ± 191 kJ; BC, 3424 ± 203 kJ; BC + 5 mg, 3125 ± 219 kJ; and BC + 10 mg, 3341 ± 200 kJ; $P = .4$). Duration of meal consumption was not significantly different between treatments and had no significant effect on EI. The VAS ratings of the appetite sensations showed no significant difference between treatments. Subjects rated the organoleptic quality of the meal as a little higher than medium, and there was no significant difference between treatments.

3.6. Adverse events

One subject vomited immediately after completion of a test day (treated with placebo). One subject reported that his mouth itched for 10 hours after ingestion of the bioactive compound. Otherwise, no subjects reported that they had illness, gastrointestinal problems, or other adverse effects in the 24 hours after the individual test days. Six cases of colds/influenza and 1 case of a broken leg occurred during the study. Test days were rescheduled in all these cases.

4. Discussion

The thermogenic effect of the present supplement seems partly to be explained by β-adrenoreceptor activation, as the thermogenic response was diminished by 50% by propranolol. As propranolol have higher affinity to β_1- and β_2-adrenoreceptors than to β_3 [36], it was not possible to confirm whether all β-adrenoreceptors were activated equally by BC or whether the β-adrenoreceptors were affected more individually. β_1- and β_2-adrenoreceptors are thought to mediate the thermogenic response [5,37,38], whereas the role of β_3-adrenoreceptor is more controversial. In rats, β_3-agonists increase EE and fat oxidation, whereas these have only weak effects in humans [5,6]. In addition, activation of α_1-adrenoreceptors has increased glucose uptake and metabolism in human adipose tissue in vivo [39].

Administration of either capsaicin or catechins in rodents or humans has led to increased sympathetic stimulation through either an increased release of NA [40] or a prolonging of the effect of NA [25]. β-Adrenergic stimulation seems to be involved in the capsaicin-induced thermogenesis, as the effect of capsaicin was inhibited by propranolol but it was not affected by the α-adrenergic antagonist phentolamine or the ganglion-blocker hexamethonium in rats [41]. This result is supported by a human study in which propranolol inhibited the thermogenic response of a capsaicin-containing meal [42]. Administration of propranolol has also diminished the thermogenic effect of GTE in rats [43], whereas the effect of caffeine on thermogenesis and lipolysis due to a postreceptor downstream action does not seem to be antagonized by a β-blockade [44]. The lesser affinity of propranolol to β_3-

adrenoreceptors may, to some extent, explain the partly blunted thermogenic response in the present study. The result is supported by the findings of Liu et al [7] who showed that the nonselective β-adrenoreceptor antagonist nadolol could reduce the thermogenic response to ephedrine by 60%. This suggests that at least 40% of the thermogenic response could be mediated by an atypical receptor, presumably the β_3-adrenoreceptor. Furthermore, the present inhibition with propranolol seems to have reached its height, as no dose-response effect of the 2 doses was seen. Thus, the halved thermogenic response after propranolol antagonism may be primarily induced by stimuli of β_3- and also α_1-adrenoreceptors, postsynaptic prolonged effect of cAMP, and adenosine antagonism. However, the α_1-adrenergic stimuli seem not to affect the whole-body thermogenesis [5,37], whereas β-adrenergic stimuli seem to increase both EE and fat oxidation [2]. A large proportion of the halved thermogenic response is probably caused by caffeine, which is known to increase sympathetic stimulation via both α- and β-adrenoreceptors. Even small doses of caffeine have the ability to both antagonize adenosine and inhibit cellular phosphodiesterase activity [33]. On the other hand, the investigated food ingredients are more rapidly absorbed than propranolol [45-47], which could disguise the contribution of the β-adrenergic stimulation to the increased metabolic rate. Tremblay et al [48] noted a substantial impact of propranolol between 90 and 180 minutes after its administration. In the present study, the suppression by propranolol seemed to be greatest between 120 and 180 minutes especially for 5 mg. Thus, the β-adrenergic stimulation may be greater than seen over the total period of 5 hours.

As EE is partly regulated by adrenergic activity, the treatment with propranolol could probably have decreased BMR in the present study. It is not possible to exclude this consequence, as an extra arm with propranolol treatment alone was not included. However, supplementation of nonselective β-antagonists seems to have only a minor effect on EE [49-51]. Two studies found no significant effect on 24-hour EE after supplementation with 240 and 160 mg propranolol per day, respectively [49,50], whereas 1 study found a 7% decline in RMR after treatment with 240 mg/d nadolol [51]. The effect of propranolol in the present study must be regarded as minimal, as only 5 and 10 mg propranolol per day were used.

The RQ was not changed by BC in the present study, which supports previous observations of the properties of the compound [10,11]. Despite inconsistencies, studies have found evidence of enhancement of fat utilization with supplementation with the present food ingredients independently: capsaicin [12,13], caffeine [20], and GTE [17,18].

The present results indicate that SBP was partly mediated by β-adrenoreceptors: BC induced a 3% SBP response that was 25% inhibited by propranolol treatments. We found no indication of β-adrenergic stimulus on DBP. The bioactive compound induced a 6% increase with or without preceding propranolol treatment. No effect of BC was observed on HR, which supports our previous findings [10,11]. Normally, one would expect an increase in EE accompanied by an increase in HR. The missing HR response to the bioactive treatment may be a consequence of the increased blood pressure, as the enhanced cardiac contractility and vasoconstriction caused by the increased smooth muscle tone may have reduced HR [52].

The present increased blood pressure is probably due mostly to caffeine. Caffeine in particular is thought to increase blood pressure and HR by enlarging the sympathetic activity mediated by α-and β-adrenergic stimuli [52-54]. However, the evidence of the effect of caffeine on these hemodynamics is inconsistent [22,23]. Furthermore, the caffeine-induced increase in blood pressure seems to be diminished by sustained caffeine intake over time [55,56], which suggests that the present adverse effect may be reduced over time. In addition, there is contradicting evidence of the effect of short- and long-term intake of catechin-caffeine mixtures on blood pressure or HR [16,17,57,58]. No other adverse effects were observed in the present study, which supports our previous findings of the good safety profile of the supplement [10,11].

A stimulation of SNS is thought to suppress hunger and enhance satiety. However, no evidence of appetite suppressant qualities of BC was found in the present study. The present results support previous findings by our group [10,11]. Treatment with 5 mg propranolol caused a significant decrease in the sensation of hunger compared with placebo. However, this was not reproduced after treatment with 10 mg. Ad libitum EI was not affected by either BC or propranolol treatment. However, the effect would be expected to be rather weak, as the treatments were given 5 and 6 hours before the ad libitum meal. The effects were probably strongly reduced, as the half-life of propranolol is 3 to 4 hours and the effect of caffeine appears to decrease 2 to 3 hours postintake [20,21,24]. Capsaicin has been observed to induce an anorectic effect in humans [14,15] and tyrosine in rats [28-30], whereas the effects of tea catechins on appetite and food intake are sparse and conflicting [19,59-61]. In addition, the organoleptic quality of the present ad libitum meal was rated as a little higher than medium and may additionally have limited the ad libitum EI test.

In conclusion, the present study confirms the thermogenic properties of the bioactive compound. The 50% reduction of the thermogenic response by propranolol indicates that β-adrenergic pathways are partly responsible for the thermogenic response.

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